II. REMARKS

Claims 47 to 60 are pending in the subject application and stand variously rejected in the outstanding Office Action. By this Amendment and Response, claims 47 to 49 and 58 have been amended. New claims 61 to 67 have been added. Support for the amendments to claims 47, 48, 49 and 58 and the addition of new claims 61 to 67 are found in the application papers on page 5, lines 23 to 28; page 8, lines 1 to 8; page 11, lines 13 to 20; and page 12, lines 3 to 31. Accordingly, an issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

The amendment of these claims is not intended to be a dedication of any subject matter of these claims. Applicants reserve the right to file one or more of the claims as originally presented in a later filed continuation application.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the outstanding objections and rejections are respectfully requested.

35 U.S.C. § 112

Claims 58-60 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Office alleged that claims 58-60 are indefinite because it is unclear if the kit of claim 58 contains any components since the word 'comprise' has been deleted from line 2 of the claim.

Claim 58 has been amended to remove the ground for rejection. In view of this amendment, reconsideration and withdrawal of the rejection is respectfully requested.

35 U.S.C. § 102

Claim 47 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wilson et al. Wilson is cited for teaching a method for screening cancer cells for sensitivity to a chemotherapeutic drug by taking a biological sample of cancer cells from a patient, (e.g., Non-Hodgkins Lymphoma) and testing for a pre-selected gene. The Office argued that

Wilson teaches that p53 overexpression was determined for tumor cells that exhibited p53 mutations, and found that 13 of 16 tumors with mutations showed p53 overexpression. Wilson also allegedly teaches that there was a very good concordance between overexpression and mutation for p53 ("wherein said genotype determines the intratumoral expression of said gene"). Wilson is alleged to further teach determining the sensitivity of tumors, which contained a good concordance between mutation and overexpression to chemotherapy. Wilson is also cited for allegedly teaching that tumors with p53 abnormality were significantly more likely to be drug resistant to EPOCH chemotherapy by both univariate and multivariate analysis, Wilson is further cited for allegedly teaching that because p53 status will likely become an important clinical parameter, the specificity and sensitivity of p53 immunochemistry was determined and found to be a reliable method of determining p53 status, and therefore a significant indicator of sensitivity to EPOCH.

Claim 47 also stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Tamiya et al. Tamiya allegedly teaches detecting two mutations in the FAS gene (pre selected gene) in samples were from PBMCs or lymph node cells. The Office state that these mutations correlated to the intratumoral expression of the gene. Tamiya allegedly further teaches that ATL samples that lacked expression of FAS antigen were resistant to anticancer drugs in vivo "correlating said gene expression to said sensitivity to said chemotherapeutic drug" and thus inherently teaches (anticipates) a method of screening cancer cells for sensitivity to a chemotherapeutic drug and correlates gene expression of a preselected gene (Fas antigen) to sensitivity to a chemotherapeutic drug.

Applicants respectfully traverse. Claim 47 has been amended to recite that the sample is from extratumoral, non-metastatic cells, e.g., hair, blood or liver. The cells can be "normal cells" (see newly added claim 64 and page 11, lines 2 to 31 of the specification). Neither Wilson et al. nor Tamiya et al. teaches that the genotype of extratumoral cells, e.g., normal cells, would be predictive of the chemotherapeutic response of the subject.

For example, Tamiya et al. specifically teaches away from such in the paragraph bridging pages 3936 to 3937 of the reference, wherein it recites that:

> "Among 47 cases examined, Fas antigen was not detected in 1 case. In contrast to ATL cell, the neutraphils of this patient expressed normal levels of Fas antigen on their surfaces, indicating that the defect in expression of Fas antigen was specific to leukemic cells (Fig. 1, case no. 2)."

For these reasons, amended claim 47 is novel over the disclosures of Wilson et al. and Tamiya et al. Reconsideration and withdrawal of the rejections is therefore respectfully requested.

Claims 57-59 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by page 102 of the New England Biolabs catalog (1996). The New England Biolabs catalog is cited for teaching a kit which contains a DNA ladder X174 DNA-Hae III Digest which containing base pairs on the order of 1,353 base pairs to 72 base pairs. The Office argued that alternatively, New England Biolabs teaches a kit which contains a DNA ladder pBR322 DNA-BstN I Digest which contains base pairs on the order of 1,857 to 13 base pairs (see page 102). The Office stated that either DNA ladders could be used as sequencing markers and appear to be a component of the kit of claim 58. The Office further noted that the use for the kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit and that, the components of the kit could be used for other processes and therefore, their dependent on the instructions of the kit.

Applicants respectfully traverse. Claims 57 to 59 specifically require that the kit contain a means for determining a genomic polymorphism of the 5 'UTR of the TS gene. Nothing in the Biolabs indicate that the markers would specifically recognize a genomic polymorphism of the 5' UTR of the TS gene. In addition, the kit requires instructions for correlating the genomic polymorphism of the 5' UTR of the TS gene to sensitivity to TS directed drug therapy. The instructions are more than an intended use. They provide the means to translate the laboratory information to its clinical relevance.

For these reasons, the rejection is in error and therefore should be reversed.

35 U.S.C. § 103

Claims 48-56 stand rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over the combination of Horie et al. and Leichman et al. in view of Ruano et al. and further in view of, in the alternative, Wilson, or Tamiya.

Horie allegedly teaches that triple tandemly repeated sequences are known to exist in the '5 terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals. Horie is also cited for teaching that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat. The Office argued that while Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility. The Office admitted that Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al. was cited for allegedly disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample (colorectal cancer biopsy) of a subject and determining the intratumoral expression of the TS gene. The Office stated that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Wilson is cited for teaching a method of screening cancer cells for sensitivity to chemotherapeutic drugs by taking a biological sample of cancer cells and determining the genotype of p53 and that the presence of mutated p53 was correlated to p53 expression. Tumors with mutated p53 were stated to exhibit p53 overexpression and significantly more resistant to treatment with EPOCH.

Tamiya is cited for teaching a method of screening cancer cells for sensitivity to chemotherapeutic drugs by taking a biological sample for cancer cells and detecting

mutations in Fas antigen. The mutations taught by Tamiya (genotype) are alleged to correlate to the intratumoral expression of the gene. The Office stated that further, Tamiya teaches that adult T cell leukemia samples that lacked expression of FAS antigen were resistant to anticancer drugs in vivo.

Ruano is cited for teaching that genetic variability is a determinant of a patient's response to therapy and that by correlating a haplotype with disease and by using genome anthologies, it is possible to create a prognostic test for customizing therapy based on a patients genotype. Ruano is also cited for teaching that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences.

The Office opined that although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening colorectal cancer cells for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for chemosensitivity of tumors to chemotherapy drugs. The Office stated that the ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to the number of TS repeats that tumor cells possessed because Ruano teaches that it is possible to create a prognostic test for customizing therapy based on a patient's genotype and Wilson teaches that identification of molecular or biological markers of drug resistance may allow for the development of a prognostic index. The Office stated that Leichman also provides motivation for screening since it allegedly teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development. The Office also noted that both Wilson and Tamiya provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected wherein the genotype determines the intratumoral expression of the gene and

correlating expression to sensitivity to the chemotherapeutic drug. The Office noted that Horie teaches that the number of repeats is associated with TS expression and therefore provide a reasonable expectation of success to screen cancer cells for sensitivity to chemotherapy drugs by determining the genotype (number of repeats in each allele) of TS wherein the genotype determines the intratumoral expression of TS and correlating gene expression to sensitivity to a chemotherapeutic drug.

Applicants respectfully traverse. The rejected claims, i.e., claims 48 to 56, depend upon amended claim 47. Claim 47 has been amended to specifically recite that the biological sample isolated from the subject to be tested be extratumoral, non-metastatic cells, e.g., normal liver cells. As stated above in reply to the rejections under 35 U.S.C. § 102, none of the primary references teach or suggest that the genotype of extratumoral, non-metastatic cells would be predictive of the subject's therapeutic response to chemotherapy. The secondary references fail to shore up this deficiency. For this reason, none of the references, alone or in combination, teaches or suggests the invention of claims 48 to 56. Reconsideration and removal of the rejection is therefore respectfully requested.

Claims 57-60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over of Horie and Leichman in view of Ruano, and further in view of Wilson or Tamiya as applied to claims 48-56 above, and further in view of Erlich (U.S. Patent 5,468,613) and the New England Biolabs catalog.

The Office relied on the teachings of Horie and Leichman in view of Ruano, and further in view of Wilson or Tamiya as set forth previously. The Office argued that although Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya do not teach a kit comprising DNA tandemly repeated sequence of the TS gene, Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays. Erlich is further cited for teaching kits which include such sequence specific oligonucleotides, and that thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct sequence specific oligonucleotides as taught by Erlich that contained tandemly repeated sequences of the TS gene for use in the method of Horie & Leichman, in view of Ruano, and further in view of

Wilson or Tamiya for the purpose of providing a sequence specific oligonucleotide that could be used to determine a tumor cell's TS genotype in the screening method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya. The motivation to provide such an oligonucleotide in kit format is the alleged need for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya more convenient to perform. The Office argued that it would have been further obvious to provide the oligonucleotides in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog.

Applicants respectfully traverse. None of the cited references, alone or in combination, teaches the necessary correlation between the genotype of the sample to be tested and the predictive response. This information is more than merely providing instructions to the user, but allows him to correlate the laboratory information to clinical relevance. None of the cited art teaches the relevance of the mutation at the 5' UTR of the TS gene to clinical responsiveness to TS-directed drug therapy. Assume for the sake of argument only, that the kit only contained information on how to carry out one or more genotyping methods. The user of the kit would be able to collect the information without understanding its clinical relevance.

For this reason, the references fail, alone or in combination, to teach or enable a necessary element of the claims. Removal of the rejection under 35 U.S.C. § 103 is therefore respectfully requested.

Supplemental Information Statement

Attached to this reply is a Supplemental Information Disclosure Statement and cited reference for consideration and entry into the application file.

III. CONCLUSION

No fee is deemed necessary in connection with the filing of this Response. However, if the Patent Office determines that an extension and/or other relief is required, Applicants

petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2518**, referencing billing number **7000722001**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Should a telephone advance prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 849-4950.

Respectfully submitted,

Date: October 28, 2004

By: _____
Antoinette F. Konski
Reg. No. 34,202

Bingham McCutchen LLP
Three Embarcadero Center, Suite 1800
San Francisco, CA 94111
Telephone: (650) 849-4950
Facsimile: (650) 849-4800